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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,792	03/28/2005	Kenji Hashimoto	2004 2053A	3058

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EXAMINER	
KINGAN, TIMOTHY G	

ART UNIT	PAPER NUMBER
1797	

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11/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,792	HASHIMOTO ET AL.	
	Examiner	Art Unit	
	TIMOTHY G. KINGAN	1797	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7-9,11-13,16 and 18-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 7-9, 11-13, 16 and 18-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1, 7-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 1, applicant recites an index in a biological sample, but does not disclose a characteristic of the biological sample that would allow a comparison of such index with that from a healthy individual or group. There must be some basis, in the identity of individuals in claim 1, even if they are selected at random from populations of affected and healthy individuals, to allow a comparison of the index with those from individuals identified as healthy or affected; otherwise the group of claim 1 is not clearly distinguished from healthy individuals or individuals with schizophrenia. Further, the index from individuals measured in claim 1 cannot be compared with the index of healthy or schizophrenic individuals, since indices from the latter two groups are not measured, or at least not claimed to be measured.

Response to Arguments

3. Applicant's arguments filed 08/28/2008 have been fully considered but they are not persuasive. Applicant's formation of an index comprising the ratio is a data processing step widely used in analysis of data from the biological and enzymological studies; such formation of ratio is commonly referred to as a "normalization", since it

returns a value for a dependent variable that reduces or normalizes the effect of a changing value of an independent variable. Schemes for normalization commonly involve dividing the raw value for a dependent variable by the value for a related independent variable known or judged to remain constant or to not be appreciably affected by conditions of an experiment (e.g., F. Strumwasser et al., U.S. Patent 5,831,074; col 8, lines 5-8). In applicant's index, the value of D-serine in samples will vary with the L-serine available for conversion by the racemase, the quantity and distribution of the racemase in the sample from which the D-serine is extracted, as well as the amount of the sample that is available and subjected to assay. The formation of a ratio of D-serine/Total serine is within the technical reach of one of ordinary skill in the art of data analysis; further, one of ordinary skill in the art would find desirable calculation of such ratio, in order to better isolate the effects of changing D-serine attributable to a change in the quantity or activity of the racemase and any amino acid oxidase or transferase that degrades D-serine, rather than a natural variability of D-serine that could occur with nutritional state or diet associated with ingestion of D- and/or L-serine.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. Claims 1, 7-9, 11-13, 16 and 18-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over G. Tsai et al., Biological Psychiatry 44:1081-1089, 1998 (herein after Tsai).

For Claim 1, Tsai teaches the step of measuring concentrations of D- and L-serine in serum of patients fulfilling the diagnosis of schizophrenia (p. 1082, col 2, ¶ 5 and p. 1083, col 2, ¶ 2). Tsai is silent on use of an index comparing D-serine to total serine. It would have been obvious to one of ordinary skill in the art at the time of invention to use such index in order to provide for uncovering the possibility that skewed values of D-serine in affected individuals (either low or high) are attributable to skewed values of total serine which would affect absolute levels of D-serine through the racemase or a serine hydroxymethyl transferase, as taught by Tsai (p. 1086, ¶ 3). Further, one of ordinary skill in the art would find desirable forming such ratio in order to evaluate and account for the effects of changes in total serine.

For Claims 7 and 8, Tsai does not teach an index that is lower than the average or the average – the standard deviation of that average calculated from healthy individuals. It

would have been obvious to one of ordinary skill in the art to use such comparisons based on averages and the statistical distributions of values comprising the averages, in order to provide for measures of statistical significance and confidence intervals readily recognized by and communicated to individuals in the practicing arts of similar fields of endeavor.

For Claim 9, Tsai is silent on an index in which comparison is to average + standard deviation of a value for individuals with schizophrenia. Such comparison would have been obvious to one of ordinary skill in the art in order to provide for an indication that a value for an affected individual falls within a range of certain confidence limits for affected individuals. Further, one of ordinary skill in the art would have found desirable such comparison in order to provide for a statistical basis for dividing affected individuals into treatment groups.

For Claims 11-12 and 19-21 Tsai teaches the steps of labeling amino acids with an amino acid labeling reagent (contacting an amino acid labeling reagent with a biological sample to label serine) comprising o-phthaldialdehyde (OPA; amino acid fluorescence-labeling reagent) by precolumn derivatization (p. 1083, col 2, ¶ 2) and fractionation of derivatized amino acids, including D-serine and L-serine (separating labeled D- and L-serine), in a reverse phase (high performance) column by liquid chromatography with quantitation by fluorescence detection (optical resolution) (p. 1083, col 2, ¶ 2).

For Claims 13, 16 and 18, Tsai is silent on separating and quantifying labeled serine by high-performance liquid chromatography before the step of separating labeled D- and L-serine. It would have been obvious to one of ordinary skill in the art at the time of

invention to use such separation and quantitation in order to prescreen samples for total serine, in a system with fewer analytical demands than those that may be required for chiral separations, for the purpose of grouping or prioritizing samples on the basis of total serine for subsequent analysis of enantiomers. Further, one of ordinary skill in the art would have found desirable to use a separation protocol comprising high-performance liquid chromatography, which fractionates on the basis of hydrophobic character of the derivatives, in order to provide for use of characterized chromatographic systems, tested for optimal combination of speed and resolution of fractionation.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Tsai as applied to claim 21 and further in view of H. Watanabe and E. Kawamura, Japanese Patent Application Publication 61-080051 (herein after Watanabe).

For Claim 22, Tsai is silent on the step of using the reagent 4-fluoro-7-nitro-2,1,3-benzoxadiazole as fluorescence-labeling reagent. Use of such reagent in amino acid analysis is known in the art; Watanabe teaches the step of using 7-fluoro-4-nitrobenzo-2-oxa-3-diazol (alternate nomenclature for the compound of the instant claim) as amino acid labeling reagent for fluorescence detection (abstract). It would have been obvious to one of ordinary skill in the art to use the reagent of Watanabe in the method of Tsai for labeling amino acids in order to provide a reactive reagent for amino acids that yields derivatives with excitation and emission spectra resolved by the optics of readily available fluorometers.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY G. KINGAN whose telephone number is (571)270-3720. The examiner can normally be reached on Monday-Friday, 8:30 A.M. to 5:00 P.M., E.S.T..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 571 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TGK

/Jill Warden/
Supervisory Patent Examiner, Art Unit 1797